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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,062	03/10/2004	Minoru Yamaguchi	OKA-0216	2613

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/796,062	YAMAGUCHI ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 25, 2008 has been entered.

Amendment Entry

2. The amendment filed June 25, 2008 has been entered. Claims 1, 7 and 9-10 have been amended. Claims 1-11 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

a) The rejection of claims 1-11 under 35 U.S.C. 112, second paragraph;

b) The rejection of claims 1-4 and 8-11 under 35 U.S.C. 102(b) as being anticipated by Bauer et al., (2000. Rapid Comm. In Mass Spectrometry. Volume 14, Issue 10, Pages 924-929);

c) The rejection of claims 1-4 and 9-11 under 35 U.S.C. 102(b) as being anticipated by Keough et al., (1999. PNAS Vol. 96:7131-7136);

d) The rejection of claims 1-11 under 35 U.S.C. 103(a) as being unpatentable over Turecek (2002. J. Mass Spectrometry. Vol. 37:1-14) in view of Keough et al., (1999. PNAS Vol. 96:7131-7136).

Response to Arguments

4. Applicant's arguments with respect to claims 1-11 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Gygi et al., (1999. Nature Biotechnology. Vol.17:994-999).

Claim 1 is drawn to a method for determining amino acid sequence of a peptide, comprising the steps of: preparing an amino acid, wherein said amino acid (a) amino acid being obtained from an α- amino acid, B-amino acid, δ-amino acid, γ-amino acid, (b) is negatively charged as a whole molecule, (c) comprises a side chain containing an

acidic group, and (d) comprises an amino group protected with a protective group which (i) prevents the amino group from becoming positively charged and (ii) maintains the negative charge of the molecule as a whole in water; preparing a peptide of interest or fragments thereof obtained by optionally cleaving the peptide of interest for reacting with said amino acid; reacting said amino acid with to the N-terminus of the peptide of interest or the fragments thereof to obtain a product peptide molecule; and subjecting the product peptide molecule to mass spectrometry analysis wherein the analysis of the mass spectra of the product peptide molecule determines the amino acid sequence of the peptide. Claim 2 is drawn to the acidic group; claim 3 is drawn to the amino acid; claims 4-6 are drawn to the protective group; claim 7 is drawn to a N-biotinylcysteic acid; claim 8 is drawn to the hydrolysis of the C-terminal side; 9 is drawn to the ionization and decay of the peptide.

Gygi et al., teach quantitative analysis of complex protein mixtures using isotope-coded affinity tags. Gygi et al., teach quantitative protein analysis are accomplished by combining protein separation, most commonly by high-resolution two-dimensional polyacrylamide gel elctrophoresis (2D-PAGE) with mass spectrometry (MS)-based or tandem mass spectrometry (MS/MS)-based sequence identification of selected separated protein species (page 994, col.1). Gygi et al., teach quantitative proteome analysis based on a class of reagents, isotope-coded affinity tags which consist of three functional elements: a specific chemical reactivity, an isotopically coded linker, and an affinity tag (page 994, col.2). Gygi et al., teach specificity toward sulfohydryl groups

with a deuterated linker, and a biotin affinity tag (page 994, col.2). Gygi et al., teach the side chains of cysteinyl residues in a reduced protein sample (page 994, col.1).

Gygi et al., teach the modification remained fairly stable and attached to the cysteinyl residues and cysteinyl residues modified by the mass of the reagents (see Figure 4). Gygi et al., teach at least one tagged cysteinyl residues and the presence of the relatively rare cysteinyl residue in a peptide adds an additional powerful constraint for database searching, tagging and selective enrichment of cysteine-containing peptides which significantly reduces the complexity of the peptide mixture containing cysteinyl residues (page 997, col.1). Gygi et al., teach significant reduction of the complexity of the peptide mixture because biotinylated cysteine-containing peptides are selectively isolated (page 998, col.1). By teaching the N-biotinylcysteic acid, Gygi et al., teach preparing an amino wherein said amino acid being obtained from an α- amino acid, B-amino acid, δ-amino acid, γ-amino acid, (b) is negatively charged as a whole molecule, (c) comprises a side chain containing an acidic group, and (d) comprises an amino group protected with a protective group which (i) prevents the amino group from becoming positively charged and (ii) maintains the negative charge of the molecule as a whole in water.

Gygi et al., teach the complexity of the mixture is reduced while protein quantification and identification are still achieved (page 998. col. 2). Gygi et al., teach powerful stabilizing agents; sensitivity of the mass spectroscopy system; and the quantification and identification of proteins that are compatible with any fractionation method which reduces complexity while quantification is maintained (page 998, col.2).

Therefore, Gygi et al., teach the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gygi et al., (1999. Nature Biotechnology. Vol.17:994-999) in view of Bauer et al., (2000. Rapid Comm. In Mass Spectrometry. Volume 14, Issue 10, Pages 924-929).

Claim 1 is drawn to a method for determining amino acid sequence of a peptide, comprising the steps of: preparing an amino acid, wherein said amino acid (a) amino acid being obtained from an α- amino acid, B-amino acid, δ-amino acid, γ-amino acid, (b) is negatively charged as a whole molecule, (c) comprises a side chain containing an acidic group, and (d) comprises an amino group protected with a protective group which (i) prevents the amino group from becoming positively charged and (ii) maintains the negative charge of the molecule as a whole in water; preparing a peptide of interest or fragments thereof obtained by optionally cleaving the peptide of interest for reacting with said amino acid; reacting said amino acid with to the N-terminus of the peptide of interest or the fragments thereof to obtain a product peptide molecule; and subjecting the product peptide molecule to mass spectrometry analysis wherein the analysis of the

mass spectra of the product peptide molecule determines the amino acid sequence of the peptide.

Claim 2 is drawn to the acidic group; claim 3 is drawn to the amino acid; claims 4-6 are drawn to the protective group; claim 7 is drawn to a N-biotinylcysteic acid; claim 8 is drawn to the hydrolysis of the C-terminal side; 9 is drawn to the ionization and decay of the peptide; claim 10 is drawn to the ionization by ionized by matrix-assisted laser desorption ionization (MALDI); and claim 11 is drawn to separation and detection by time-of-flight mass spectrometry (TOFMS).

Gygi et al., has been discussed above for teaching a method for determining amino acid sequence of a peptide, comprising the steps of: preparing an amino acid, wherein said amino acid (a) amino acid being obtained from an α- amino acid, B-amino acid, δ-amino acid, γ-amino acid, (b) is negatively charged as a whole molecule, (c) comprises a side chain containing an acidic group, and (d) comprises an amino group protected with a protective group which (i) prevents the amino group from becoming positively charged and (ii) maintains the negative charge of the molecule as a whole in water; preparing a peptide of interest or fragments thereof obtained by optionally cleaving the peptide of interest for reacting with said amino acid; reacting said amino acid with to the N-terminus of the peptide of interest or the fragments thereof to obtain a product peptide molecule; and subjecting the product peptide molecule to mass spectrometry analysis wherein the analysis of the mass spectra of the product peptide molecule determines the amino acid sequence of the peptide; However Gygi et al., does not teach the ionization by ionized by MALDI or separation and detection by TOFMS.

Bauer et al., teach a method for determining amino acid sequence of a peptide, comprising: preparing a peptide of interest by cleaving the peptide of interest; coupling an amino acid derivative to the N-terminus of the peptide of interest, wherein the amino acid derivative having protected an amino group with a protective group and derived from an amino acid with a side chain containing an acidic group; and subjecting the coupled product to mass spectrometry analysis (abstract). Bauer et al., teach the model peptide was oxidized with performic acid to convert the cysteine to cysteic acid, analyzed by mass spectrometry (page 925, col.1). Bauer et al., teach the sulfonic acid derivatization of the N-terminus using chlorosulfonylacetyl chloride and performic acid oxidation of cysteine were carried out (page 925, col. 1). Bauer et al., teach the N-terminal acid group being generated by converting the side chain of the cysteine to cysteic acid by exposure to performic acid (page 926, col. 1). The acidic group of cysteic acid is a sulfo group and the amino acid is cysteic acid. Bauer et al., teach the use of highly acidic, N-terminal derivatives simplifies the interpretation of fragment ion spectra for peptide ions produced by ionization techniques (page 924, col. 2). Bauer et al., teach derivatization techniques has improved the quality of PSD-MADLI spectra (page 924, col.2). Bauer et al., teach sequence information is provided when techniques involve using a protease (page 924, col.1). Tryptic digests have the advantage of producing peptides possessing a basic residue at their C-terminus (page 924, col. 1).

Therefore it would have been prima facie obvious at the time of applicants invention to incorporate TOFMS as taught by Bauer et a., to the method for determining amino acid sequence of a peptide comprising an amino acid wherein the (a) amino acid

being obtained from an α- amino acid, B-amino acid, δ-amino acid, γ-amino acid, (b) is negatively charged as a whole molecule, (c) comprises a side chain containing an acidic group, and (d) comprises an amino group protected with a protective group which (i) prevents the amino group from becoming positively charged and (ii) maintains the negative charge of the molecule as a whole in water as taught by Gygi et al., in order to provide an improved mass spectrometric spectrum using N-biotinylcysteic acid. One of ordinary skill in the art would have a reasonable expectation of success modifying the method of determination as taught by Gygi et al., because Gygi et al., already teach that derivatization ensures selective conjugation of the N-terminal cysteine while protecting the amino group and Bauer et al., teach considerable enhancement within the mass spectra result. Furthermore, no more than routine skill would have been required to use an amino acid derivative with a side chain having an acidic group since Gygi et al., this technique is well known to aide in the complete sequencing of the peptide using mass spectrometric analysis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keough et al., (1999. PNAS Vol. 96:7131-7136) in view of Gygi et al., (1999. Nature Biotechnology. Vol.17:994-999).

Claim 1 is drawn to a method for determining amino acid sequence of a peptide, comprising the steps of: preparing an amino acid, wherein said amino acid (a) amino acid being obtained from an α- amino acid, B-amino acid, δ-amino acid, γ-amino acid, (b) is negatively charged as a whole molecule, (c) comprises a side chain containing an acidic group, and (d) comprises an amino group protected with a protective group which (i) prevents the amino group from becoming positively charged and (ii) maintains the negative charge of the molecule as a whole in water; preparing a peptide of interest or fragments thereof obtained by optionally cleaving the peptide of interest for reacting with said amino acid; reacting said amino acid with to the N-terminus of the peptide of interest or the fragments thereof to obtain a product peptide molecule; and subjecting the product peptide molecule to mass spectrometry analysis wherein the analysis of the mass spectra of the product peptide molecule determines the amino acid sequence of the peptide.

Claim 2 is drawn to the acidic group; claim 3 is drawn to the amino acid; claims 4-6 are drawn to the protective group; claim 7 is drawn to a N-biotinylcysteic acid; claim 8 is drawn to the hydrolysis of the C-terminal side; 9 is drawn to the ionization and decay of the peptide; claim 10 is drawn to the ionization by ionized by matrix-assisted laser desorption ionization (MALDI); and claim 11 is drawn to separation and detection by time-of-flight mass spectrometry (TOFMS).

Keough et al., teach a method for determining amino acid sequence of a peptide, comprising the steps of: preparing a peptide of interest obtained by cleaving the peptide of interest; coupling an amino acid derivative to the N-terminus of the peptide of interest wherein the amino acid derivative has a protected amino group with a protective group and derived from an amino acid with a side chain containing an acidic group; and subjecting the coupled product to mass spectrometry analysis (page 7132). Keough et al., teach a method involves the addition of a strong acid group (amino acid derivative) Keough et al., teach considerable enhancement of the N-terminal ion after enhancement which aided in the complete sequencing of the peptide (page 7133, col.1). Keough et al., teach procedures for high-sensitivity tryptic peptide sequencing using Matrix-Assisted Laser Desorption Ionization Spectrometry Post Source Decay (PSD MALDI) and routes to produce tryptic peptides containing an N-terminal sulfonic acid. The peptide of interest has been cleaved with a tryptic enzyme before coupling the N-terminus of the peptide.

Keough et al., teach the N-terminal derivatization procedures involve coupling an amino acid derivative to the N terminus of peptides (page 7132, col.1). This derivatization reaction introduces an aromatic sulfonic acid group directly at the N terminus of the peptide (page 7133, col.2). Keough et al., also teach peptides derivatized with carboxylic acids (page 7132, col.1). Therefore Keough et al., teach a derivative derived from an amino acid with a side chain containing an acidic group such as a sulfo group found on cysteic acid. Keough et al., teach the PSD MALDI analysis of a commercially available peptide, CDPGYIGSR (page 7133, col.1). Keough et al., also

teach analysis with Time-of-Flight mass (TOF) spectrometry (page 7131, col.1). Keough et al., shows in the lower drawing of Fig. 1, an improved spectrum after oxidation of the N-terminal cysteine to cysteic acid and the complete sequence of the peptide could be determined by PSD MALDI after oxidation (page 7133, col. 1). Keough et al., teach that PSD MALDI mass spectrometry was developed for high-sensitivity peptide sequencing applications has become an increasingly essential tool for protein and peptide sequencing because of its speed, sensitivity, and applicability to analyze complex mixtures (page 7131, col.1).

However Keough et al., do not specifically teach an amino acid, wherein said amino acid (a) amino acid being obtained from an α- amino acid, B-amino acid, δ-amino acid, γ-amino acid, (b) is negatively charged as a whole molecule, (c) comprises a side chain containing an acidic group, and (d) comprises an amino group protected with a protective group which (i) prevents the amino group from becoming positively charged and (ii) maintains the negative charge of the molecule as a whole in water;

Gygi et al., has been discussed above for teaching a method for determining amino acid sequence of a peptide, comprising the steps of: preparing an amino acid, wherein said amino acid (a) amino acid being obtained from an α- amino acid, B-amino acid, δ-amino acid, γ-amino acid, (b) is negatively charged as a whole molecule, (c) comprises a side chain containing an acidic group, and (d) comprises an amino group protected with a protective group which (i) prevents the amino group from becoming positively charged and (ii) maintains the negative charge of the molecule as a whole in water; preparing a peptide of interest or fragments thereof obtained by optionally

cleaving the peptide of interest for reacting with said amino acid; reacting said amino acid with to the N-terminus of the peptide of interest or the fragments thereof to obtain a product peptide molecule; and subjecting the product peptide molecule to mass spectrometry analysis wherein the analysis of the mass spectra of the product peptide molecule determines the amino acid sequence of the peptide.

Therefore it would have been prima facie obvious at the time of applicants invention to add of the amino acid of Gygi et al., to the method for determining amino acid sequence of a peptide, comprising preparing the amino acid; preparing the peptide of interest; reacting the amino acid with the N-terminus of the peptide; subject the product peptide to mass spectrometry analysis wherein the analysis determines the amino acid sequence as taught by Keough et al., in order to provide an improved mass spectrometric spectrum using the amino acid of Gygi et al. One of ordinary skill in the art would have a reasonable expectation of success modifying the method of determination as taught by Keough et al., because Keough et al., already teach that derivatization ensures selective conjugation of the N-terminal cysteine while protecting the amino group and teach considerable enhancement within the mass spectra result; while Gygi e al., teach additional powerful constraint for database searching, tagging and selective enrichment of cysteine-containing peptides while significantly reducing the complexity of the peptide mixture containing cysteinyl residues. Furthermore, no more than routine skill would have been required to use an amino acid of Gygi et al., with a since both Keough et al., and Gygi et al., this technique is well known to aide in the

complete sequencing of the peptide using mass spectroscopy and MALDI-TOF analysis.

Conclusion

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645